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DOI:
10.1097/PSY.0b013e31819d1910

Document Version
Peer reviewed version

Citation for published version (Harvard):
Gallagher, S, Phillips, A, Drayson, M & Carroll, D 2009, 'Caregiving for Children With Developmental Disabilities Is Associated With a Poor Antibody Response to Influenza Vaccination', *Psychosomatic Medicine*, vol. 71, no. 3, pp. 341-344. https://doi.org/10.1097/PSY.0b013e31819d1910

Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009). Caregiving for children with developmental disabilities is associated with a poor antibody response to influenza vaccination *Psychosomatic Medicine,* 71, 341-344. DOI: 10.1097/PSY.0b013e31819d1910. http://dx.doi.org/10.1097/PSY.0b013e31819d1910

Caregiving for children with developmental disabilities is associated with a poor antibody response to influenza vaccination

Running head: Antibody response to vaccination

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Word Count 3479

2 Figures

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Abstract

Objective: Older spousal caregivers of dementia patients have been found to show a relatively poor antibody response to medical vaccination. The present case control study compared the antibody responses to vaccination of younger parental caregivers of children with developmental disabilities and parents of typically developing children. **Methods:** At baseline assessment, 32 parents of children with developmental disabilities and 29 parents of typically developing children completed standard measures of perceived stress and child problem behaviours. They also provided a blood sample and were then vaccinated with the thymus-dependent trivalent influenza vaccine. Further blood samples were taken at 1- and 6-month follow-ups. **Results**: Relative to parents of typically developing children (mean titre = 458, SD = 155.7 at 1-month and mean titre = 265, SD = 483.0 at 6-month follow-up) caregivers (mean titre = 219, SD = 528.4 at 1-month and 86, SD = 55.0 at 6-month) mounted a poorer antibody response than controls to the B/Malaysia strain of the vaccine. It was those caregivers reporting more child problem behaviours that tended to show the weakest antibody response. **Conclusion:** The negative impact of caregiving on antibody response to vaccination would not appear to be restricted to older spousal caregivers, but is also evident in younger parents caring for children with developmental disabilities. The behavioural characteristics of the care recipients may be a determinant of whether or not antibody response to vaccination is compromised.

Keywords: antibody response; caregiving; children with developmental disabilities; child problem behaviours; chronic stress; influenza vaccination

INTRODUCTION

In humans, the effects of chronic stress on immunity have been studied by comparing caregivers who provide care to sick or disabled relatives with broadly matched controls (1-6) and the antibody response to vaccination is regarded as a useful model for the studying the effects of stress in this context (7-9). Older spousal caregivers of dementia patients have been found to show a relatively poor antibody response to both influenza and pneumococcal vaccinations (5, 10, 11), implying a reduced capacity to fight viral and bacterial infections. However, younger caregivers have rarely been studied in this context.

Only two studies have examined these younger caregiver cohorts, with mixed results (12, 13). Caregivers of multiple sclerosis patients did not differ from controls in antibody response to the influenza vaccination (13). This raises the issue of whether the poor antibody response observed in older caregivers is a function of an interaction between chronic stress exposure and immunosenescence, (14, 15) and will be less likely to occur in younger caregivers. We have postulated that rather than immunosenescence, it is possible that it is the intensity of the chronic stress experienced that determines the influence of caregiving on immunity. The precise caregiving experience may vary between those caring for patients with multiple sclerosis and dementia. Indeed, older spousal caregivers of dementia patients have been found to report greater distress than younger multiple sclerosis caregivers (13). A model that would help us to test these hypotheses is parents' caregiving for children with developmental disabilities. Dealing with severe cognitive difficulties and behaviours that are problematic and distressing are the main challenges for both parents of children with developmental disabilities (16, 17) and caregivers of dementia patients (18, 19). In addition, caring for someone with a mental health problem has been found to be more stressful than caring for someone with a physical health problem (e.g., cancer) (19), a likely consequence of the repetitive challenges faced by such caregivers on a daily basis. In our recent study we demonstrated that parents of children with developmental disabilities mounted a poorer response to a pneumococcal vaccination (12)

The pneumococcal vaccination is a thymus-independent bacterial vaccine; the formation of antigen-specific antibodies does not require and cannot receive the help of T-cells. Influenza and other viral vaccines are thymus-dependent and require the

help of T-cells for antibody production. It has yet to be demonstrated that the antibody response to a thymus-dependent vaccination is compromised in younger caregivers. Consequently, we compared the antibody responses to the trivalent thymus-dependent influenza vaccine in relatively young parents caring for children with developmental disabilities and parents caring for typically developing children. It was hypothesised that parents of children with developmental disabilities would report substantially more distress and mount a poorer antibody response.

METHOD

Participants

A more detailed description of some of the methodology is available elsewhere, as we have previously reported differences between these caregivers and controls in antibody response to pneumococcal vaccination (12). Thirty-two parents caring for children with developmental disabilities and 29 parents of typically developing children participated. All parents were volunteers recruited through media campaigns and those contacting were informed that is was a study examining antibody response to vaccination in parents of children with developmental disabilities and parents of typically developing children. Inclusion criteria for these parents were: caring for at least one child with Autism, Downs, Cornelia de Lange, or Smith-Magenis syndromes; children had to be aged between 3 and 19 years and cared for at home during the school term. The majority of parents reported caring for a child with Autism (66%); the remainder were caring for a child with Downs (22%) or with other syndromes (12%). Controls were parents of typically developing children. No parent had received the influenza vaccine previously or had a history of negative reactions to blood sampling (e.g., fainting). Attempts were made to match the groups on age, sex, socioeconomic position, ethnicity, and marital status. The study was approved by the appropriate Medical Research Ethics committee and all participants provided informed consent.

Study design and procedure

Participants were tested between December 2006 and December 2007. At baseline, parents completed questionnaires and then provided a blood sample to determine baseline antibody status. After medical screening, they were vaccinated

with the 2006/07 season Inflexal influenza vaccine (Sanofi Pasteur, MSD) containing A/New Caledonia/20/99 (H1N1), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/2004-like virus strains. Follow-up blood samples were collected 1-month (N = 60) and 6-months later (N = 57). One caregiving parent relocated and was therefore unable to attend their next appointments; the remaining parents who were not available for the final follow-up cited issues of family commitments as the main reason for non-attendance.

Questionnaires

Psychological stress over the previous month was measured using the 14-item Perceived Stress Scale (20). The 25-item Strengths and Difficulties Questionnaire (21) was used to assess child problem behaviours. Parents are asked to rate whether a behaviour is somewhat true, 0, true, 1, or certainly true, 2, of their child, with higher scores indicating more problem behaviour. Examples include 'often fights with other children and bullies them' and some items are reversed scored (e.g. generally obedient, usually does what adults request). The scale has been shown to be reliable (Cronbach's $\alpha = .76$) and effective at identifying behavioural problems in children (22). Internal consistency for the scale in this study was .88. As in our previous research (23-25), typical health behaviours were assessed at baseline, using a questionnaire adapted from the Whitehall II study (26).

Blood sampling and antibody analysis

Anti-influenza antibody titres were measured in venous blood by Glaxo SmithKline Beecham (Dresden, Germany), using a haemagglutination inhibition test (WHO). The antibody results are reported as titres; a titre represents the reciprocal of the highest dilution having a positive response in the haemagglutination inhibition assay.

Statistical analyses

Given a degree of skew in these data, all analyses were performed on $\log_{10}$ antibody levels. Repeated measures ANCOVA was used to test whether the groups differed at follow-up; since interest lay in the antibody response, baseline $\log_{10}$ antibody titre was entered as a covariate as in our previous studies (24, 27). Partial eta-squared (η^2) is reported as a measure of effect size. Further ANCOVAs were

undertaken to adjust for possible confounders and test for possible mediators. Hierarchical linear regression analyses were used within the caregiving group to determine whether perceived stress, child problem behaviour, or age was associated with antibody response.

RESULTS

Demographics and psychosocial status

The summary characteristics of the caregivers and controls are presented elsewhere (12). Caregivers and controls were well-matched on most variables and did not differ on health behaviours. However, parents of children with developmental disabilities were found to differ on the following age, (mean = 42.8, SD = 5.95, and mean = 39.9, SD = 4.35, for the caregivers and controls respectively), F (1,57) = 4.44, p = .04; child's age, (mean 11.5, SD = 3.41, and mean = 8.8, SD = 4.22, respectively), F (1,57) = 7.18, p = .01, and hours spent caregiving each day, (mean = 10.6, SD = 8.19, and mean = 3.5 , SD = 3.53, respectively), F (1,56) = 17.89, p <.001. Parents of children with developmental disabilities also reported higher perceived stress (mean = 30.3, SD = 8.40, and mean = 22.2, SD = 7.48), for the caregivers and controls respectively), F (1,57) = 15.52, p <.001, and more child problem behaviours, (mean = 23.0, SD = 5.97, and mean = 9.9, SD= 4.89, respectively), F (1,57) = 84.64, p <.001.

Caregiving and Antibody response

The mean (SE) antibody titre for each of the influenza strains at each time point for caregivers and controls is displayed in Figure 1. ANCOVA revealed highly significant variations in $\log_{10}$ antibody titre over time for each strain: A/New Caledonia, $F(2, 53) = 138.35$, $p < .001$, $\eta^2 = .719$; A/Wisconsin, $F(2, 53) = 72.19$, $p < .001$, $\eta^2 = .572$; B/Malaysia, $F(2, 53) = 226.74$, $p < .001$, $\eta^2 = .808$. After adjusting for $\log_{10}$ baseline antibody levels, ANCOVA revealed a main effect of group on $\log_{10}$ antibody response for the B/Malaysia strain, $F(1,53) = 4.22$, $p = .04$, $\eta^2 = .074$, with caregivers mounting a poorer response. There were no significant group effects for A/New Caledonia or A/Wisconsin. The group effect for the B/Malaysia withstood adjustment for age of parents and children and time spent caregiving, $F(1,49) = 4.92$, $p = .03$, $\eta^2 = .091$. However, in models in which perceived stress and child problem behaviour were also entered, the group effect was no longer significant, F(1,48) =

3.67, $p = .06$, $\eta^2 = .071$, and $F(1,47) = 3.32$, $p = .07$, $\eta^2 = .066$, respectively. This suggests that at least some of the group variation in antibody response is determined by variations in perceived stress and child problem behaviour. In terms of non-responsiveness, 19% of caregivers compared to only 6% of controls failed to mount a four-fold increase in B/Malaysia tires at 1-month.

[Insert Figure 1 about here]

Within caregivers

In hierarchical linear regression analyses, again adjusting for baseline titre, no significant associations emerged between perceived stress and child problem behaviours and antibody response to the B/Malaysia strain. However, there were indications of a negative relationship between child problem behaviour and 6-month antibody response, $\beta = -.32$, $t = -1.67$, $p = .10$, $\Delta R^2 = .10$. To illustrate this effect we divided caregivers into those reporting high and low behaviour problems using a median split (see Figure 2). Finally, we examined the association between age of caregivers and their antibody response to the B/Malaysia strain. There was a tendency for older caregivers to mount a poorer antibody response at 1-month, $\beta = -.33$, $t = -1.87$, $p = .07$, $\Delta R^2 = .11$.

[Insert Figure 2 about here]

DISCUSSION

Compared to parents of typically developing children, young parents caring for children with developmental disabilities mounted a poor antibody response to the B/Malaysia strain of the influenza vaccine. The present findings are consistent with those of studies of older spousal caregivers (5, 11). They also extend our results with the thymus-independent pneumococcal vaccine (12), implying that these relatively young parental caregivers may have a reduced ability to fight both bacterial and viral infections. The present study reinforces the hypothesis that an ageing immune system is not a pre-requisite for a poor response to medical vaccination in caregivers. Nevertheless, older caregivers tended to have a poorer antibody response to B/Malaysia at 1-month, suggesting that we cannot dismiss the hypothesis that chronic

stress and immunosenescence may have synergistic effects (14). Whether or not caregivers exhibit a poor antibody response to vaccination would seem to depend on the characteristics of the caregiving experience rather than caregiving *per se*. This could explain the difference between our findings and an earlier report that younger spousal caregivers of multiple sclerosis patients did not differ from controls in their antibody response to influenza vaccination (13). A comparison of perceived stress scores between studies revealed that the present caregivers experienced much more stress than those caring for spouses with multiple sclerosis (12).

It would also appear that some influenza strains are more susceptible than others to psychosocial influence. Such specificity has been reported in previous studies of influenza vaccination (5, 25, 28). It is difficult at this stage to determine why particular vaccine strains are sensitive to certain types of psychosocial influence. One explanation for such specificity is that less immunogenic antigens are more susceptible to exogenous influence (9). Alternatively, strain novelty is another characteristic of antigens that may underlie such specificity. For example, the negative effects of psychological stress on the antibody response to the trivalent influenza vaccination were observed for viral strains recently introduced to the vaccine (5, 25, 29). It is worth noting that the A/New Caledonia strain has been a component of the northern hemisphere influenza vaccine since 2004, and thus current rates of naturalistic exposure are likely to be high and novelty is likely to be lower in the present study. In contrast, examination of the B strains comprising the influenza vaccination in previous years (B/Shanghai) indicates that the B/Malaysia is a novel component in the current vaccine. Further, although parents reported not having any previous influenza vaccines, prior exposure cannot be ruled out and epidemiological evidence shows that the majority of circulating viruses in Europe in the year prior to the study were closely related to A/Caledonia (H1N1) and antigenically related to A/Wisconsin (H3N2) (30), thus increasing the antigenic novelty of the B/Malaysia strain.

Adjustment for perceived stress and child problem behaviour attenuated the group differences in antibody response to the B/Malaysia strain and caregivers reporting more child problem behaviour tended to mount a poorer antibody response. This finding is consistent with our results for pneumococcal vaccination (12) and broadly in line with the results of research with caregivers of patients with mental health difficulties using other health indicators (18, 19, 31, 32). Further, interventions for

managing and preventing care recipients' behaviour problems were found to enhance caregivers' immunity immediately after intervention and 6-months later (33). Taken together, these data indicate that problem behaviours may be a key determinant of caregivers' health and that interventions targeting such behaviours may bring health benefits.

The present study has a number of limitations. Our sample size might be regarded as small, but it is the same order of magnitude as other case-control vaccination studies (10, 13). There is also the possibility of confounding as a result of unmeasured variables or imperfect matching among participants. However, our main findings survived statistical adjustment for a number of potential confounders.

In summary, the negative impact of caregiving on antibody response to vaccination is not restricted to older spousal caregivers, but is also evident in younger parents caring for children with developmental disabilities. Nor is it restricted to thymus-independent antigens. Finally, it would appear that the behavioural characteristics of care recipients may influence whether or not antibody response to vaccination is compromised in their caregivers.

Conflict of interest: The authors have no conflicts of interest to declare and the study was funded by the University of Birmingham.

References

1. Kiecolt-Glaser JK, Glaser R, Shuttleworth EC, Dyer CS, Ogrocki P, Speicher CE. Chronic stress and immunity in family caregivers of Alzheimer's disease victims. Psychosom Med 1987;49:523-35.
2. Kiecolt-Glaser JK, Dura JR, Speicher CE, Trask OJ, Glaser R. Spousal caregivers of dementia victims: longitudinal changes in immunity and health. Psychosom Med 1991;53:345-62.
3. Mills PJ, Adler KA, Dimsdale JE, Perez CJ, Ziegler MG, Ancoli-Israel S, Patterson TL, Grant I. Vulnerable caregivers of Alzheimer disease patients have a deficit in beta 2-adrenergic receptor sensitivity and density. Am J Geriatr Psychiatry 2004;12:281-6.
4. Redwine L, Mills PJ, Sada M, Dimsdale J, Patterson T, Grant I. Differential immune cell chemotaxis responses to acute psychological stress in Alzheimer caregivers compared to non-caregiver controls. Psychosom Med 2004;66:770-5.
5. Vedhara K, Cox NK, Wilcock GK, Perks P, Hunt M, Anderson S, Lightman SL, Shanks NM. Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. Lancet 1999;353:627-31.
6. Vitaliano PP, Scanlan JM, Ochs HD, Syrjala K, Siegler IC, Snyder EA. Psychosocial stress moderates the relationship of cancer history with natural killer cell activity. Ann Behav Med 1998;20:199-208.
7. Vedhara K, Fox JD, Wang EC. The measurement of stress-related immune dysfunction in psychoneuroimmunology. Neurosci Biobehav Rev 1999;23:699-715.
8. Burns VE, Carroll D, Ring C, Drayson M. Antibody response to vaccination and psychosocial stress in humans: relationships and mechanisms. Vaccine 2003;21:2523-34.
9. Cohen S, Miller GE, Rabin BS. Psychological stress and antibody response to immunization: a critical review of the human literature. Psychosom Med 2001;63:7-18.
10. Glaser R, Sheridan J, Malarkey WB, MacCallum RC, Kiecolt-Glaser JK. Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. Psychosom Med 2000;62:804-7.

11. Kiecolt-Glaser JK, Glaser R, Gravenstein S, Malarkey WB, Sheridan J. Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc Natl Acad Sci U S A 1996;93:3043-7.
12. Gallagher S, Phillips AC, Drayson MT, Carroll D. Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. Brain Behav Immun in press.
13. Vedhara K, McDermott MP, Evans TG, Treanor JJ, Plummer S, Tallon D, Cruttenden KA, Schifitto G. Chronic stress in nonelderly caregivers: psychological, endocrine and immune implications. J Psychosom Res 2002;53:1153-61.
14. Graham JE, Christian LM, Kiecolt-Glaser JK. Stress, age, and immune function: toward a lifespan approach. J Behav Med 2006;29:389-400.
15. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci U S A 2003;100:9090-5.
16. Floyd FJ, Gallagher EM. Parental stress, care demands, and use of support services for school-age children with disabilities and behavior problems. Family Relations 1997;46:359-71.
17. Hastings RP, Daley D, Burns C, Beck A. Maternal distress and expressed emotion: cross-sectional and longitudinal relationships with behavior problems of children with intellectual disabilities. Am J Ment Retard 2006;111:48-61.
18. Pinquart M, Sorensen S. Differences between caregivers and noncaregivers in psychological health and physical health: a meta-analysis. Psychol Aging 2003;18:250-67.
19. Pinquart M, Sorensen S. Associations of stressors and uplifts of caregiving with caregiver burden and depressive mood: a meta-analysis. J Gerontol B Psychol Sci Soc Sci 2003;58:P112-28.
20. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24:385-96.
21. Goodman R. The Strengths and Difficulties Questionnaire: a research note. J Child Psychol Psychiatry 1997;38:581-6.
22. Goodman R, Scott S. Comparing the Strengths and Difficulties Questionnaire and the Child Behavior Checklist: is small beautiful? J Abnorm Child Psychol 1999;27:17-24.

23. Burns VE, Carroll D, Drayson M, Whitham M, Ring C. Life events, perceived stress and antibody response to influenza vaccination in young, healthy adults. J Psychosom Res 2003;55:569-72.
24. Gallagher S, Phillips AC, Ferraro AJ, Drayson MT, Carroll D. Psychosocial factors are associated with the antibody response to both thymus-dependent and thymus-independent vaccines. Brain Behav Immun 2008;22 456-60.
25. Phillips AC, Burns VE, Carroll D, Ring C, Drayson M. The association between life events, social support, and antibody status following thymus-dependent and thymus-independent vaccinations in healthy young adults. Brain, Behav, Immun 2005;19:325-33.
26. Marmot MG, Dowey Smith G, Stansfeld S, Patel C, North F, Head J, White I, Brunner E, Feeney A. Health inequalities among British civil servants: the Whitehall II study. Lancet 1991;337:1387–93.
27. Gallagher S, Phillips AC, Ferraro AJ, Drayson MT, Carroll D. Social support is positively associated with the immunoglobulin M response to vaccination with pneumococcal polysaccharides. Biol Psychol 2008;78 211-5.
28. Pressman SD, Cohen S, Miller GE, Barkin A, Rabin BS, Treanor JJ. Loneliness, social network size, and immune response to influenza vaccination in college freshmen. Health Psychol 2005;24:297-306.
29. Miller GE, Cohen S, Pressman S, Barkin A, Rabin BS, Treanor JJ. Psychological stress and antibody response to influenza vaccination: when is the critical period for stress, and how does it get inside the body? Psychosom Med 2004;66:215-23.
30. World Influenza Centre. Influenza activity 2008: accessed on 3/11/08.
31. Dyck DG, Short R, Vitaliano PP. Predictors of burden and infectious illness in schizophrenia caregivers. Psychosom Med 1999;61:411-9.
32. Mausbach BT, Patterson TL, Rabinowitz YG, Grant I, Schulz R. Depression and distress predict time to cardiovascular disease in dementia caregivers. Health Psychol 2007;26:539-44.
33. Garand L, Buckwalter KC, Lubaroff D, Tripp-Reimer T, Frantz RA, Ansley TN. A pilot study of immune and mood outcomes of a community-based intervention for dementia caregivers: the PLST intervention. Arch Psychiatr Nurs 2002;16:156-67.

Figure 1. Mean (SE) antibody titre for the three vaccine strains for caregivers and controls at baseline, 1-month and 6-months.

Figure 2. Mean (SE) B/Malaysia $\log_{10}$ antibody titre at 6-month follow-up, adjusted for baseline antibody titre, for caregivers reporting high and low child problem behaviour.